11-03-04

IAW DAC

PATENT
Docket No. 554792000401

CERTIFICATE OF EXPRESS MAIL

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10, **LABEL NO. EV 470 627 243 US** on the date indicated below and is addressed to: **COMMISSIONER FOR PATENTS, MS: PETITIONS, P.O. BOX 1450, Alexandria, VA 22313-1450.**

Dated: November 1, 2004 **Signature:** **(Lilia Olsen)**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Allen I. BAIN et al.

Serial No.: 10/674,684

Filing Date: September 29, 2003

For: ION CHANNEL MODULATING COMPOUNDS AND USES THEREOF

11/04/2004 HALI11 00000023 031952 10674684

01 FC:1460 130.00 DA

Examiner: R. Anderson

Group Art Unit: 1626

PETITION UNDER 37 CFR 1.182 TO CORRECT RESPONSE TO NOTICE OF OMITTED ITEM(S) FILED September 10, 2004

MS: PETITIONS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

A Notice of Omitted Items (Notice) was mailed to Applicants in the above-captioned patent application on August 16, 2004. The Notice stated that pages 53, 59, 61, 63, 64, 79, 91, 102, and 132 of the specification were omitted when filed in the U.S. Patent and Trademark Office on September 29, 2003. Applicants filed a response and petition to the Notice of Omitted Items on September 10, 2004. The petition was granted on October 6, 2004.

In the response and petition of September 10, 2004, Applicants erroneously filed pages 53, 59, 61, 63, 64, 79, 91, 102, and 132 of U.S. Application No. 09/283,873, a priority document

to U.S. Application No. 10/674,684, instead of pages 53, 59, 61, 63, 64, 79, 91, 102, and 132 of U.S. Application No. 10/674,684. Applicants respectfully request that the enclosed pages 53, 59, 61, 63, 64, 79, 91, 102, and 132 of U.S. Application No. 10/674,684 be substituted in the Specification in place of the pages incorrectly included in the response of September 10, 2004. Pages 53, 59, 61, 63, 64, 79, 91, 102, and 132 are attached as **Exhibit A**. It is further noted that U.S. Application 09/680,988 (the parent application for the present application, from which the specification of the present application is based) was expressly incorporated by reference in the present application with the preliminary amendment filed on September 29, 2003.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **554792000401**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: November 1, 2004

Respectfully submitted,

By: Michael R Ward

Michael R. Ward
Registration No. 38,651

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Please type a plus sign inside this box → [+]

PTO/SB/21 (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	**10/674,684**
Filing Date	September 29, 2003
First Named Inventor	Allan I. BAIN
Group Art Unit	1626
Examiner Name	R. Anderson
Total Number of Pages in This Submission: 14	Attorney Docket Number: **554792000401**

ENCLOSURES (*check all that apply*)

[X] **Fee Transmittal Form - 1 pg IN DUPL**	[ ] Assignment Papers *(for an Application)*	[ ] After Allowance Communication to Group
[ ] Amendment/Reply	[ ] Licensing-related Papers	[ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
[ ] After Final	[X] **Petition - UNDER 37 CFR 1.182 - 2 pgs**	[ ] Proprietary Information
[ ] Extension of Time Request - 1 pg	[ ] **Power of Attorney - 1 pg**	[X] Other Enclosure(s) *(please identify below)*
[ ] Express Abandonment Request	[ ] Terminal Disclaimer	**1. EXHIBIT TAB A: copies of Specification pages 53, 59, 61, 63, 64, 79, 91, 102 and 132 - 9 pgs**
[ ] Information Disclosure Statement	[ ] Request for Refund	
[ ] Certified Copy of Priority Document(s)	[ ] CD, Number of CD(s) _____	**RETURN RECEIPT POSTCARD**
[ ] Response to Missing Parts/ Incomplete Application	Remarks	
[ ] Response to Missing Parts under 37 CFR 1.52 or 1.53		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual Name	**MICHAEL R. WARD (38,651)** **MORRISON & FOERSTER LLP** **CUSTOMER 20872**
Signature	Michael R Ward
Date	**November 1, 2004**

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Dated: November 1, 2004 **Signature:** _____ **(Lilia Olsen)**

SF-1807757

EV470627243US

PTO/SB/17 (10-04)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2005

Effective 10/01/2004. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 130.00

Complete if Known	
Application Number	10/674,684
Filing Date	September 29, 2003
First Named Inventor	Alan I. BAIN
Examiner Name	R. Anderson
Art Unit	1626
Attorney Docket No.	554792000401

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit Card ☐ Money Order ☒ Other ☐ None

☒ **Deposit Account:**

Deposit Account Number: 03-1952

Deposit Account Name: Morrison & Foerster LLP

The Director is authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	790	2001	395	Utility filing fee	
1002	350	2002	175	Design filing fee	
1003	550	2003	275	Plant filing fee	
1004	790	2004	395	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) -0-

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

		Extra Claims		Fee from below		Fee Paid
Total Claims	- ** =		x		=	
Independent Claims	- ** =		x		=	
Multiple Dependent					=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	88	2201	44	Independent claims in excess of 3
1203	300	2203	150	Multiple dependent claim, if not paid
1204	88	2204	44	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) -0-

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	430	2252	215	Extension for reply within second month	
1253	980	2253	490	Extension for reply within third month	
1254	1,530	2254	765	Extension for reply within fourth month	
1255	2,080	2255	1,040	Extension for reply within fifth month	
1401	340	2401	170	Notice of Appeal	
1402	340	2402	170	Filing a brief in support of an appeal	
1403	300	2403	150	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,370	2501	685	Utility issue fee (or reissue)	
1502	490	2502	245	Design issue fee	
1503	660	2503	330	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	130.00
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37CFR 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
Other fee (specify)					

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 130.00

CUSTOMER NO: 20872

SUBMITTED BY					(Complete *(if applicable)*)
Name (Print/Type)	MICHAEL R. WARD	*Registration No. (Attorney/Agent)*	38/651	*Telephone*	415/268-6237
Signature	Michael R Ward			*Date*	November 1, 2004

would be chosen to enhance bioavailability or stability of the compound for the appropriate mode of employment (*e.g.*, oral or parenteral routes of administration).

A composition intended to be administered by injection can be prepared by combining the cyclohexylamine compound with water, and preferably buffering agents, so as to form a solution. The water is preferably sterile pyrogen-free water. A surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the cyclohexylamine compound so as to facilitate dissolution or homogeneous suspension of the cyclohexylamine compound in the aqueous delivery system. Surfactants are desirably present in aqueous compositions of the invention because the cyclohexylamine compounds of the present invention are typically hydrophobic. Other carriers for injection include, without limitation, sterile peroxide-free ethyl oleate, dehydrated alcohols, propylene glycol, as well as mixtures thereof.

Suitable pharmaceutical adjuvants for the injecting solutions include stabilizing agents, solubilizing agents, buffers, and viscosity regulators. Examples of these adjuvants include ethanol, ethylenediaminetetraacetic acid (EDTA), tartrate buffers, citrate buffers, and high molecular weight polyethylene oxide viscosity regulators. These pharmaceutical formulations may be injected intramuscularly, epidurally, intraperitoneally, or intravenously.

Pharmacological Testing

As noted above, the present invention provides for utilizing the compounds described above in *in vitro* and *in vivo* methods. In one embodiment, ion channels, such as cardiac sodium channels, are blocked *in vitro* or *in vivo*.

Ion channels are ubiquitous membrane proteins in the cells of warm-blooded animals such as mammals. Their critical physiological roles include control of the electrical potential across the membrane, mediation of ionic and fluid balance, facilitation of neuromuscular and neuronal transmission, rapid transmembrane signal transduction, and regulation of secretion and contractility.

light, and/or sealed from contact with ambient air, and/or formulated with suitable coatings or excipients.

The following examples are offered by way of illustration and not by way of limitation. In the Examples, and unless otherwise specified, starting materials were obtained from well-known commercial supply houses, *e.g.*, Aldrich Chemical Company (Milwaukee, WI), and were of standard grade and purity. "Ether" and "ethyl ether" each refers to diethyl ether; "h." refers to hours; "min." refers to minutes; "GC" refers to gas chromatography; "v/v" refers to volume per volume; and ratios are weight ratios unless otherwise indicated.

was heated to 80°C and then the temperature reduced to 40°C. The resulting yellow solution was poured into ice-water (1500 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (500 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 13.4 g of an amber oil which was dissolved in water (150 mL) and the pH of the solution was adjusted to pH 2 with aqueous 1M HCl. The acidic aqueous solution was extracted with ethyl ether (2 x 100 mL) and then basified to pH 10 with 50% sodium hydroxide aqueous solution. The basic aqueous solution was extracted with ethyl ether (2 x 100 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 7.16 g of the crude free aminoether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with a mixture of ethyl acetate-chloroform (1:1, v/v) as eluent to yield 4.37 g of the pure free base. The product was dissolved in ethyl ether (80 mL) and converted to the monohydrochloride salt by adding saturated solution of HCl in ethyl ether (80 mL). An oil came out of the solution, the solvent was evaporated *in vacuo* and the residue dissolved in the minimum amount of warm ethyl alcohol, addition of a large volume of ethyl ether triggered crystallization. The crystals were collected to afford 3.83 g (31% yield) of the title compound, m.p. 158-160°C, having the elemental analysis indicated in Table 1.

EXAMPLE 2

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(1-NAPHTHENETHOXY)]CYCLOHEXANE MONOHYDROCHLORIDE

(COMPOUND #2)

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (6.0 g, 32 mmol) and triethylamine (6.8 mL, 48 mmol) in dichloromethane (100 mL) was added via cannula a solution of methanesulfonyl chloride (3.10 mL, 40 mmol) in dichloromethane (50 mL). The addition was completed

crystallization. The crystals were collected to afford 2.30 g of the title compound, m.p. 198-200°C, having the elemental analysis indicated in Table 1.

EXAMPLE 3

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(4-BROMOPHENETHOXY)]CYCLOHEXANE MONOHYDROCHLORIDE

(COMPOUND #3)

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (25 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (25 mL). The addition was completed in 5 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 2 hours. The reaction mixture was diluted with dichloromethane (50 mL) and washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (25 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 4.7 g of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.62 g, 25.8 mmol) in dry dimethylformamide (25 mL) was added via cannula a solution of 4-bromophenethylalcohol (4.0 g, 20 mmol) in dimethylformamide (50 mL). Addition was followed by evolution of gas and the reaction mixture was stirred at room temperature for 4 hours. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the slurry of alcoholate. The reaction mixture was heated to 80°C for 2 hours, then the temperature was reduced to 35°C and the reaction stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (150 mL) and

dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 7.4 g of an oil which was dissolved in ether (80 mL) was treated with a saturated solution of HCl in ether. An oil came out of solution, the solvent was evaporated *in vacuo* and the residue was dissolved in water (100 mL). The acidic aqueous solution was extracted with ethyl ether (2 x 50 mL) and then basified to pH 10 with 50% sodium hydroxide aqueous solution. The basic aqueous solution was extracted with ethyl ether (2 x 50 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 3.67 g of the crude free amino ether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with a mixture of ethyl acetate-dichloromethane (1:1, v/v) as eluent to provide the pure free base. The product was dissolved in ethyl ether (30 mL) and converted to the monohydrochloride salt by adding a saturated solution of HCl in ethyl ether (30 mL). The solvent was evaporated and the residue dissolved in the minimum amount of ethyl alcohol, addition of a large volume of ethyl ether triggered crystallization. The crystals were collected to afford 1.31 g of the title compound, m.p. 148-151°C, having the elemental analysis indicated in Table 1.

EXAMPLE 4

(±)-TRANS-[2-(4-MORPHOLINYL)-1-[2-(2-NAPHTHOXY)ETHOXY)]CYCLOHEXANE MONOHYDROCHLORIDE

(COMPOUND #4)

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 10 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 4 hours. The dichloromethane mixture was washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL).

EXAMPLE 14

(1R,2R)/(1S,2S)-2-(4-MORPHOLINYL)-1-(3,4-DICHLOROPHENETHOXY) CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #14)

The basic overall approach used to synthesize this compound is analogous to that shown in Figure 1.

(i) (1R,2R)/(1S,2S)-2-(4-Morpholinyl)cyclohexanol: A mixture of cyclohexene oxide (206.5 mL, 2 mol, 98%) and morpholine (175 mL, 2 mol) in water (60 mL) was refluxed for 3.5 h. Morpholine (5.3 mL) was added to the reaction mixture, which was then further refluxed for 1.5 h. in order to complete the reaction. The cooled reaction mixture was then partitioned between 40% NaOH aqueous solution (100 mL) and diethyl ether (200 mL). The aqueous layer was separated from the organic layer and extracted twice more with diethyl ether (2 x 100 mL). The combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*. Vacuum distillation yielded 342.3 g (92.4%) of the title compound.

(ii) To a chilled (0°C) solution of (1R,2R)/(1S,2S)-2-(4-morpholinyl)cyclohexanol (40.76 g, 0.22 mol) and triethylamine (36.60 mL, 0.26 mol) in dichloromethane (400 mL) was added dropwise a solution of methanesulfonyl chloride (20.53 mL, 0.26 mol) in dichloromethane (50 mL). The reaction mixture was stirred at 0°C for 45 min. and then at room temperature for 3 hours. The reaction mixture was then washed with water (2 x 100 mL); the combined washings were back-extracted with dichloromethane (100 mL). The combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield the crude mesylate suitable for the next step without any further purification.

(iii) 3,4-Dichlorophenethyl alcohol: To a solution of lithium aluminum hydride (7.79 g, 195 mmol) in anhydrous diethyl ether (435 mL) was added slowly as a powder, via a solid dropping funnel, 3,4-dichlorophenyl acetic acid (27.20 g, 130 mmol). When the addition was completed, the reaction mixture was refluxed for 12 hours. The reaction was quenched by cautious addition of saturated sodium sulfate

dichloromethane (10 mL). The acidic aqueous solution was extracted once more with dichloromethane (10 mL), the combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*. Recrystallization from a mixture of ethanol-hexanes yielded 636 mg (38% yield) of the title compound, having the elemental analysis indicated in Table 1.

EXAMPLE 20

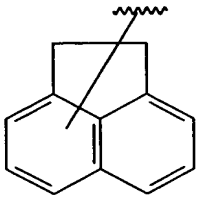
(1R,2R)/(1S,2S)-2-(3-KETOPYRROLIDINYL)-1-[3-(CYCLOHEXYL)PROPOXY]CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND #20)

(i) 3-Cyclohexyl-1-propyl bromide: To the chilled (0°C) 3-cyclohexyl-1-propanol (5 g, 35.15 mmol) was added slowly a solution of phosphorus tribromide (1.1 mL, 17.6 mmol) in dichloromethane (2 mL). Upon completion of the addition, the reaction mixture was allowed to warm up to room temperature and was stirred for 4 hours. The reaction was quenched by addition of saturated sodium bicarbonate aqueous solution (5 mL) and 10% NaOH (10 mL). The resulting mixture was extracted with diethyl ether (3 x 50 mL), the combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to provide an oil. Vacuum distillation yielded 3.4 g (47% yield) of the title compound.

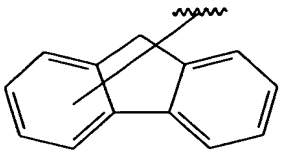
(ii) (1R,2R)/(1S,2S)-2-[1,4-Dioxa-7-azaspiro[4.4]non-7-yl]-1-[3-(cyclohexyl)propoxy]cyclohexane: To a suspension of sodium hydride (200 mg, 8.33 mmol) in anhydrous dimethylformamide (20 mL) was added a solution of (1R,2R)/(1S,2S)-2-(1,4-dioxa-7-azaspiro[4.4]non-7-yl)cyclohexanol (1.5 g, 6.6 mmol) in anhydrous dimethylformamide (10 mL). The resulting mixture was stirred at room temperature for 30 min. and then a solution of 3-(cyclohexyl)propyl bromide (1.67 g, 8.15 mmols) in anhydrous dimethylformamide was quickly added. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into water (200 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were back-washed with brine (50 mL) and the solvent was evaporated

diluted to 50 mL with water and extracted twice with diethyl ether (2 x 50 mL) and then thrice with dichloromethane (3 x 50 mL). The combined dichloromethane extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*, the residual oil was further dried by azeotropic distillation of toluene. The title compound was crystallized by triturating in hexanes (430 mg, 93% yield), and has elemental analysis indicated in Table 1.

where R_{12} is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2-C_7alkanoyloxy, C_1-C_6alkyl, C_1-C_6alkoxy, C_2-C_7alkoxycarbonyl, C_1-C_6thioalkyl, and $N(R_{15},R_{16})$ where R_{15} and R_{16} are independently selected from hydrogen, acetyl, methanesulfonyl, and C_1-C_6alkyl; and Z is selected from CH, CH_2, O, N and S, where Z may be directly bonded to "X" as shown in formula (I) when Z is CH or N, or Z may be directly bonded to R_{17} when Z is N, and R_{17} is selected from hydrogen, C_1-C_6alkyl, C_3-C_8cycloalkyl, aryl and benzyl;



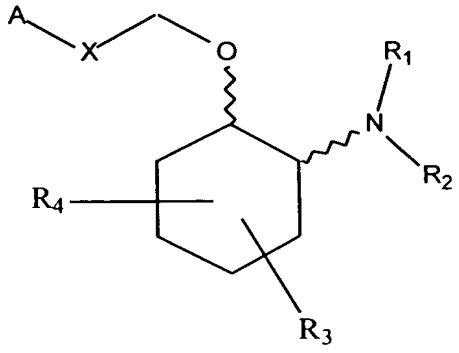
(VII)



(VIII)

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

50. A compound according to claim 49 having formula (IX), or a solvate or pharmaceutically acceptable salt thereof:



(IX)

wherein, independently at each occurrence,